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L7	l2 near8 l3	760	L7
L6	l2 with l3	1371	L6
L5	l3 and l4	1	L5
L4	l1 and L2	1	L4
L3	enzyme	210391	L3
L2	gene adj therapy	31002	L2
L1	6083725.pn.	1	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 20 of 29 returned.

1. 20050153934. 24 Nov 04. 14 Jul 05. Chaperone-based therapy for Niemann-Pick disease. Schuchman, Edward H., et al. 514/78; 514/114 A61K031/685.

2. 20050112113. 22 Oct 04. 26 May 05. Presbyopia treatment by lens alteration. Till, Jonathan S., et al. 424/94.1; 424/427 A61K038/43 A61F002/14.

3. 20050101677. 14 Dec 04. 12 May 05. Presbyopia treatment by lens alteration. Till, Jonathan S.. 514/706; 514/762 604/20 A61K031/095 A61K031/01 A61N001/30.

4. 20050031591. 04 Oct 04. 10 Feb 05. Tumor-specific promotor and use thereof. Hamada, Katsuyuki. 424/93.2; 435/235.1 435/456 A61K048/00 C12N007/00 C12N015/861.

5. 20040213774. 18 Jan 02. 28 Oct 04. Presbyopia treatment by lens alteration. Till, Jonathan S.. 424/94.4; 514/18 514/706 604/20 A61K038/44 A61K038/05 A61K031/095 A61F002/00.

6. 20040204379. 16 Jan 04. 14 Oct 04. Combination enzyme replacement, gene therapy and small molecule therapy for lysosomal storage diseases. Cheng, Seng H., et al. 514/44; A61K048/00.

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9. 20030157065. 10 Apr 03. 21 Aug 03. Tumor-specific promoters. Tagawa, Masatoshi. 424/93.2; 435/320.1 435/456 A61K048/00 C12N015/86.

10. 20030013642. 30 Aug 02. 16 Jan 03. Hemoglobin-haptoglobin complexes. Adamson, J. Gordon, et al. 514/6; 530/385 A61K038/42.

11. 20020110549. 18 Jan 02. 15 Aug 02. Presbyopia treatment by lens alteration. Till, Jonathan S.. 424/94.4; 514/18 514/706 604/20 A61K038/44 A61K038/05 A61K031/095 A61F002/00.

12. 20020095135. 19 Jun 01. 18 Jul 02. Combination enzyme replacement, gene therapy and small molecule therapy for lysosomal storage diseases. Meeker, David, et al. 604/522; A61M031/00.

13. 20020076787. 29 Mar 01. 20 Jun 02. Transiently immortalized cells for use in gene therapy. Baetge, Edward E., et al. 435/199; 424/188.1 435/456 C12N015/867 C12N009/22.

14. 20020025311. 16 Aug 01. 28 Feb 02. Presbyopia treatment by lens alteration. Till, Jonathan S.. 424/94.1; 514/18 514/47 604/20 A61K038/43 A61N005/067 A61K038/06 A61K031/7105.

15. 20020025306. 05 Jan 01. 28 Feb 02. Methods of increasing the glucose responsiveness of pancreatic ss-cells. Baetge, Edward E., et al. 424/93.21; 435/366 A61K048/00 C12N005/08.

16. 20010031741. 06 Feb 01. 18 Oct 01. Methods for treatment of lysosomal storage diseases. Ziegler, Robin, et al. 514/44; 424/94.61 514/102 A61K048/00 A61K038/47 A61K031/663.

17. 6923955. 18 Jan 02; 02 Aug 05. Presbyopia treatment by lens alteration. Till; Jonathan S., et al. 424/78.04;. A61K03174.

18. 6890948. 08 Apr 03; 10 May 05. Use of indole-3-acetic acid derivatives in medicine. Wardman; Peter, et al. 514/419;. A61K03140.

19. 6841565. 31 Mar 03; 11 Jan 05. Treatment of patients with chronic lymphocytic leukemia. Lucas; David M., et al. 514/346; 514/352 514/357. A61K031/44.

20. 6518062. 10 Sep 98; 11 Feb 03. Enzyme combinations for destroying proliferative cells. Blanche; Francis, et al. 435/320.1; 424/93.2 424/93.6 435/194 435/325 435/455 435/69.1 435/69.7 514/44 536/23.2 536/23.4 536/23.5. C12N015/00 C12N005/00 C07H021/04 A01N063/00 A61K031/70.

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Terms	Documents
combin$ near8 L7	29

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Search Results - Record(s) 21 through 29 of 29 returned.

☐ 21. 6479637. 30 Apr 99; 12 Nov 02. Hemoglobin-haptoglobin complexes. Adamson; J. Gordon, et al. 530/385; 424/193.1 424/194.1. A61K035/14 A61K039/385 A61K038/16 C07K001/00.

☐ 22. 6451601. 29 Mar 01; 17 Sep 02. Transiently immortalized cells for use in gene therapy. Baetge; Edward E., et al. 435/366; 435/377 435/405 530/350 536/23.4. C12N005/08.

☐ 23. 6358739. 10 Apr 00; 19 Mar 02. Transiently immortalized cells. Baetge; Edward E., et al. 435/377; 530/350. C12N005/08.

☐ 24. 6331528. 25 Apr 00; 18 Dec 01. Method for treatment in gene therapy and use of guanine derivative therefor. Ono; Nobukazu. 514/44; 424/93.6 435/320.1 514/45. A61K031/70 C12N015/00 A01N063/00.

☐ 25. 6319905. 19 May 99; 20 Nov 01. Method of controlling L-Dopa production and of treating dopamine deficiency. Mandel; Ronald J., et al. 514/44; 424/93.1 424/93.2 424/93.6 435/320.1 536/23.5. A01N043/04 A01N063/00 A61K048/00 C07H021/04 C12N015/00.

☑ 26. 6207648. 17 Jul 98; 27 Mar 01. Methods of using cytochrome P450 reductase for the enhancement of P450-based anti-cancer gene therapy. Waxman; David J., et al. 514/44; 435/320.1 435/455 536/23.2 536/23.4. A01N043/04 C12N015/00 C12N015/63 C07H021/04.

☐ 27. 6066624. 15 Feb 96; 23 May 00. Gene therapy for solid tumors using adenoviral vectors comprising suicide genes and cytokine genes. Woo; Savio L. C., et al. 514/44; 424/93.2. A61K048/00.

☐ 28. 5817796. 05 May 95; 06 Oct 98. C-myb ribozymes having 2'-5'-linked adenylate residues. Stinchcomb; Dan T., et al. 536/24.5; 435/6 435/91.31 536/23.1 536/23.2. C07H021/04 C12Q001/68.

☐ 29. 5646042. 13 Jan 95; 08 Jul 97. C-myb targeted ribozymes. Stinchcomb; Dan T., et al. 435/366; 435/320.1 435/325 435/353 435/6 435/91.31 514/44 536/23.1 536/23.2 536/24.5. C12N005/22 C12N005/16 C12N009/22 C12Q001/68.

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Terms	Documents
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L3         1164 S L1(8A)L2
L4           55 S COMBIN?(8A)L3
L5           29 DUP REM L4 (26 DUPLICATES REMOVED)

=> d au ti so pi 1-29 l5

L5   ANSWER 1 OF 29  CAPLUS  COPYRIGHT 2005 ACS on STN
IN   Schuchman, Edward H.; Desnick, Robert J.
TI   Active site-specific chaperone-based therapy for Niemann-Pick disease
     associated with mutation in acid sphingomyelinase (ASM) gene
SO   PCT Int. Appl., 64 pp.
     CODEN: PIXXD2
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     --------------      ----   --------    --------------------    --------
PI   WO 2005051331        A2    20050609    WO 2004-US41345         20041124
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO,
             SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
     US 2005153934         A1    20050714    US 2004-998270          20041124

L5   ANSWER 2 OF 29  CAPLUS  COPYRIGHT 2005 ACS on STN
IN   Fan, Jian-Quiang
TI   Combination therapy for treating protein deficiencies
SO   PCT Int. Appl., 40 pp.
     CODEN: PIXXD2
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     --------------      ----   --------    --------------------    --------
PI   WO 2004074450        A2    20040902    WO 2004-US4909          20040218
     WO 2004074450        C1    20041104
         W:  AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,
             BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,
             CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,
             ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
             IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC,
             LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,
             MZ, MZ, NA, NI
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
             BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG
     US 2004219132         A1    20041104    US 2004-781356          20040217

L5   ANSWER 3 OF 29  CAPLUS  COPYRIGHT 2005 ACS on STN
IN   Cheng, Seng H.; Meeker, David
TI   Combined enzyme replacement, gene
     therapy and small molecule therapy for lysosomal storage diseases
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SO U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S. Ser. No. 884,526.
CODEN: USXXCO

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004204379	A1	20041014	US 2004-758773	20040116
US 2002095135	A1	20020718	US 2001-884526	20010619

L5 ANSWER 4 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AU Searle, Peter F.; Chen, Ming-Jen; Hu, Longqin; Race, Paul R.; Lovering, Andrew L.; Grove, Jane I.; Guise, Chris; Jaberipour, Mansooreh; James, Nicholas D.; Mautner, Vivien; Young, Lawrence S.; Kerr, David J.; Mountain, Andrew; White, Scott A.; Hyde, Eva I.
TI Nitroreductase: A prodrug-activating enzyme for cancer gene therapy
SO Clinical and Experimental Pharmacology and Physiology (2004), 31(11), 811-816
CODEN: CEXPB9; ISSN: 0305-1870

L5 ANSWER 5 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AU Hajri, Amor; Wack, Severine; Lehn, Pierre; Vigneron, Jean-Pierre; Lehn, Jean-Marie; Marescaux, Jacques; Aprahamian, Marc
TI Combined suicide gene therapy for pancreatic peritoneal carcinomatosis using BGTC liposomes
SO Cancer Gene Therapy (2004), 11(1), 16-27
CODEN: CGTHEG; ISSN: 0929-1903

L5 ANSWER 6 OF 29 MEDLINE on STN DUPLICATE 1
AU Grove Jane I; Lovering Andrew L; Guise Christopher; Race Paul R; Wrighton Christopher J; White Scott A; Hyde Eva I; Searle Peter F
TI Generation of Escherichia coli nitroreductase mutants conferring improved cell sensitization to the prodrug CB1954.
SO Cancer research, (2003 Sep 1) 63 (17) 5532-7.
Journal code: 2984705R. ISSN: 0008-5472.

L5 ANSWER 7 OF 29 MEDLINE on STN DUPLICATE 2
AU Cowen Rachel L; Patterson Adam V; Telfer Brian A; Airley Rachel E; Hobbs Steve; Phillips Roger M; Jaffar Mohammed; Stratford Ian J; Williams Kaye J
TI Viral delivery of P450 reductase recapitulates the ability of constitutive overexpression of reductase enzymes to potentiate the activity of mitomycin C in human breast cancer xenografts.
SO Molecular cancer therapeutics, (2003 Sep) 2 (9) 901-9.
Journal code: 101132535. ISSN: 1535-7163.

L5 ANSWER 8 OF 29 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 3
AU Cygan, Zygmunt [Reprint Author]; Cygan, Wieslaw
TI Cancers and anaerobic clostridium.
Original Title: Nowotwory zlosliwe a beztlenowce clostridium..
SO Medycyna Weterynaryjna, (2003) Vol. 59, No. 9, pp. 758-761. print.
ISSN: 0025-8628 (ISSN print).

L5 ANSWER 9 OF 29 MEDLINE on STN DUPLICATE 4
AU Baldwin Alex; Huang Zeqi; Jounaidi Youssef; Waxman David J
TI Identification of novel **enzyme**-prodrug **combinations** for use in cytochrome P450-based **gene therapy** for cancer.
SO Archives of biochemistry and biophysics, (2003 Jan 1) 409 (1) 197-206.
Journal code: 0372430. ISSN: 0003-9861.

L5 ANSWER 10 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
IN Tagawa, Masatoshi
TI Use of tumor-specific promoters of human midkine gene and c-erbB-2 gene in cancer gene therapy
SO PCT Int. Appl., 54 pp.

CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002010368	A1	20020207	WO 2001-JP6228	20010718
W: AU, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
AU 2001072750	A5	20020213	AU 2001-72750	20010718
EP 1302539	A1	20030416	EP 2001-951914	20010718
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
US 2003157065	A1	20030821	US 2003-333013	20030410

L5 ANSWER 11 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AU Baldwin, Alex; Huang, Zeqi; Jounaidi, Youssef; Waxman, David J.
TI Identification of novel **enzyme**-prodrug **combinations** for use in cytochrome P450-based **gene therapy** for cancer
SO Archives of Biochemistry and Biophysics (2002), Volume Date 2003, 409(1), 197-206
CODEN: ABBIA4; ISSN: 0003-9861

L5 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
IN Meeker, David; Cheng, Seng H.
TI **Combination enzyme** replacement, **gene therapy** and small molecule therapy for lysosomal storage diseases
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001097829	A2	20011227	WO 2001-US19579	20010619
WO 2001097829	A3	20021227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

L5 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
IN Mandel, Ronald J.; Leff, Stuart E.
TI Method of controlling L-dopa production and of treating dopamine deficiency
SO U.S., 13 pp.
CODEN: USXXAM

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6319905	B1	20011120	US 1999-314790	19990519

L5 ANSWER 14 OF 29 LIFESCI COPYRIGHT 2005 CSA on STN
AU Huang, Z.; Waxman, D.J.
TI Modulation of cyclophosphamide-based cytochrome P450 gene therapy using liver P450 inhibitors
SO Cancer Gene Therapy [Cancer Gene Ther.], (20010600) vol. 8, no. 6, pp. 450-458.
ISSN: 0929-1903.

L5 ANSWER 15 OF 29 MEDLINE on STN DUPLICATE 5
AU Greco O; Rossiter S; Kanthou C; Folkes L K; Wardman P; Tozer G M; Dachs G U

TI Horseradish peroxidase-mediated gene therapy: choice of prodrugs in oxic and anoxic tumor conditions.
SO Molecular cancer therapeutics, (2001 Dec) 1 (2) 151-60.
Journal code: 101132535. ISSN: 1535-7163.

L5 ANSWER 16 OF 29 MEDLINE on STN DUPLICATE 6
AU Greco O; Folkes L K; Wardman P; Tozer G M; Dachs G U
TI Development of a novel **enzyme**/prodrug **combination** for **gene therapy** of cancer: horseradish peroxidase/indole-3-acetic acid.
SO Cancer gene therapy, (2000 Nov) 7 (11) 1414-20.
Journal code: 9432230. ISSN: 0929-1903.

L5 ANSWER 17 OF 29 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Springer C J
TI Suicide **gene therapy** with new **enzyme**/prodrug **combinations**.
SO HUMAN GENE THERAPY, (20 MAR 1999) Vol. 10, No. 5, pp. 845-845.
ISSN: 1043-0342.

L5 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AU Marveggio, S.; Raic, S.; Pongracic, M.; Mintas, M.; Pilger, B.; Wurth, C.; Folkers, G.; Scapozza, L.
TI 9-(2-Hydroxypropyl)adenine: a novel fraudulent substrate of HSV1-thymidine kinase. An interdisciplinary study
SO Proceedings of ECSOC-1: The First International Electronic Conference on Synthetic Organic Chemistry; [and] Proceedings of ECSOC-2: The Second International Electronic Conference on Synthetic Organic Chemistry, Sept. 1-30, 1997, 1998 (1999), Meeting Date 1997-1998, 568-577. Editor(s): Lin, Shu-Kun; Pombo-Villar, Esteban. Publisher: Molecular Diversity Preservation International, Basel, Switz.
CODEN: 69ASBO

L5 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AU Hamstra, Daniel A.; Rice, David J.; Pu, Anthony; Oyedijo, Dotun; Ross, Brian D.; Rehemtulla, Alnawaz
TI Combined radiation and enzyme/prodrug treatment for head and neck cancer in an orthotopic animal model
SO Radiation Research (1999), 152(5), 499-507
CODEN: RAREAE; ISSN: 0033-7587

L5 ANSWER 20 OF 29 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Greco, O.; Dachs, G. U.; Wardman, P.; Folkes, L. K.; Chaplin, D. J.
TI Development of an **enzyme**/prodrug **combination** for **gene therapy** of cancer.
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 478. print.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research. Philadelphia, Pennsylvania, USA. April 10-14, 1999. American Association for Cancer Research.
ISSN: 0197-016X.

L5 ANSWER 21 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AU Raic-Malic, S.; Mintas, M.
TI Antiherpes virus agents
SO Kemija u Industriji (1999), 48(7-8), 297-304
CODEN: KJUIAR; ISSN: 0022-9830

L5 ANSWER 22 OF 29 MEDLINE on STN DUPLICATE 7
AU Christians F C; Scapozza L; Crameri A; Folkers G; Stemmer W P
TI Directed evolution of thymidine kinase for AZT phosphorylation using DNA

family shuffling.
SO Nature biotechnology, (1999 Mar) 17 (3) 259-64.
Journal code: 9604648. ISSN: 1087-0156.

L5 ANSWER 23 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
IN Blanche, Francis; Cameron, Beatrice; Couder, Michel; Crouzet, Joel
TI Enzyme combinations for producing toxic nucleoside triphosphate analogs for destroying proliferative cells
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9735024	A1	19970925	WO 1997-FR436	19970312
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2746016	A1	19970919	FR 1996-3267	19960315
FR 2746016	B1	19980417		
CA 2248629	AA	19970925	CA 1997-2248629	19970312
AU 9721642	A1	19971010	AU 1997-21642	19970312
AU 732432	B2	20010426		
EP 910654	A1	19990428	EP 1997-914376	19970312
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BR 9708194	A	19990727	BR 1997-8194	19970312
JP 2000507814	T2	20000627	JP 1997-533187	19970312
ZA 9702247	A	19970917	ZA 1997-2247	19970314
NO 9804132	A	19980908	NO 1998-4132	19980908
US 6518062	B1	20030211	US 1998-125576	19980910

L5 ANSWER 24 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AU Paillard, Florence
TI Bystander effects in enzyme/prodrug gene therapy
SO Human Gene Therapy (1997), 8(15), 1733-1735
CODEN: HGTHE3; ISSN: 1043-0342

L5 ANSWER 25 OF 29 MEDLINE on STN DUPLICATE 8
AU Green N K; Youngs D J; Neoptolemos J P; Friedlos F; Knox R J; Springer C J; Anlezark G M; Michael N P; Melton R G; Ford M J; Young L S; Kerr D J; Searle P F
TI Sensitization of colorectal and pancreatic cancer cell lines to the prodrug 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB1954) by retroviral transduction and expression of the E. coli nitroreductase gene.
SO Cancer gene therapy, (1997 Jul-Aug) 4 (4) 229-38.
Journal code: 9432230. ISSN: 0929-1903.

L5 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
IN Tiraby, Gerard; Reynes, Jean-Paul; Tiraby, Michele; Cazaux, Christophe; Drocourt, Daniel
TI Gene therapy by activation of combinations of pyrimidine nucleoside and nucleobase analogs with fusion proteins of activating enzymes
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9616183	A1	19960530	WO 1995-FR1511	19951116
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5856153	A	19990105	US 1994-343923	19941117

AU 9641809	A1	19960617	AU 1996-41809	19951116
EP 792369	A1	19970903	EP 1995-940324	19951116
EP 792369	B1	20000405		
R: BE, CH, DE, ES, FR, GB, IT, LI, NL				
ES 2146788	T3	20000816	ES 1995-940324	19951116

L5 ANSWER 27 OF 29 MEDLINE on STN DUPLICATE 9
AU Kelly M A; Vestling M M; Murphy C M; Hua S; Sumpter T; Fenselau C
TI Primary structure of bovine adenosine deaminase.
SO Journal of pharmaceutical and biomedical analysis, (1996 Aug) 14 (11) 1513-9.
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L5 ANSWER 28 OF 29 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
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L5 ANSWER 16 OF 29 MEDLINE on STN DUPLICATE 6
AB This paper demonstrates the potential for utilizing the plant enzyme, horseradish peroxidase (HRP), in a gene-directed enzyme prodrug therapy context. Human T24 bladder carcinoma cells transfected with a mammalian expression vector containing the HRP cDNA were selectively sensitized to the nontoxic plant hormone, indole-3-acetic acid (IAA). The HRP/IAA-induced cell kill was effective in normoxic and anoxic conditions. The activated drug is a long-lived species able to cross cell membranes, and cell contact appears not to be required for a bystander effect to take place. These preliminary results suggest that the delivery of the HRP gene to human tumors followed by IAA treatment may provide a novel cancer gene-directed enzyme prodrug therapy approach, with potential to target hypoxic cells.

L5 ANSWER 17 OF 29 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

L5 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AB Herpes simplex virus type 1 thymidine kinase (HSV1 TK) phosphorylates thymidine (dT) to thymidine monophosphate (dTMP) which plays a key role in reactivation from the latency and replication of herpes simplex viruses. Acyclovir (ACV) and gancyclovir (GCV) are today the only therapeutic compds. to interfere with a severe HSV infection. Those mols. act as

fraudulent substrates blocking virus proliferation by dead end complexes with the viral DNA after being inactivated by the HSV-specific TK. Furthermore, HSV1 TK was more recently used as a suicide **enzyme** in **gene therapy** of cancer and AIDS in **combination** with ACV. The mol. basis of the selective therapy, that uses HSV1 TK as target, is the difference in substrate specificity between the human cellular and the herpes viral TK isoenzymes. Because of the important therapeutic implications, HSV is not only linked to viral infection but also with other diseases such as Kaposi's sarcoma and Alzheimer's disease, and the increase of resistance towards ACV and GCV. Intensive efforts have been directed towards the search for new compds. with antiviral activity. The results of a first cycle of structure-based drug-design with the goal of developing new compds. for antiviral and gene therapy, are reported. Findings suggest that 9-(2-hydroxypropyl)adenine could possibly be a fraudulent substrate of TK.

L5 ANSWER 19 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AB In an effort to improve the therapeutic outcome for squamous cell cancer of the head and neck, we have used the enzyme cytosine deaminase (CD) and the prodrug 5-fluorocytosine (5-FC) as a means to deliver the chemotherapeutic agent 5-fluorouracil (5-FU) in a tumor-specific manner and have evaluated the use of this treatment in combination with external-beam radiation. Infection of SCCVII cells in culture with a CD-expressing retrovirus and treatment with 5-FC was cytotoxic depending on the time of treatment and dose of 5-FC. An orthotopic model of squamous cell cancer of the head and neck was used in vivo to study the CD/5-FC system both alone and with concurrent radiation due to the radiosensitizing properties that 5-FU generates in situ. Treated mice were imaged using magnetic resonance imaging (MRI), and their survival was evaluated. Neither 5-FU nor radiation either alone or combined provided a survival advantage. In contrast, 5-FC treatment prolonged survival and decreased tumor burden compared to control animals, but the tumors recurred after the treatment ceased. Finally, combined treatment with concurrent administration of 5-FC and radiation resulted in a synergistic decrease in tumor growth and enhanced survival over treatment with 5-FC or radiation alone.

L5 ANSWER 20 OF 29 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

L5 ANSWER 21 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AB Main problems in antiviral chemotherapy generally and therapy against herpes viruses are described in the introductory part of the paper. Furthermore, description of icosahedral and helical structure of the virus is given. Herpes virus diseases in man caused by herpes simplex virus type 1 (HSV 1), herpes simplex virus type 2 (HSV 2), varicella zoster virus (VZV), Epstein Barr virus (EBV), cytomegalovirus (CMV) and human herpes virus 6 (HHV 6) are also reported. Antiherpes drugs that are representatives of different classes of compds. such as 5-substituted deoxyuridines, arabinonucleosides, acylonucleosides and phosphonomethoxypurine and pyrimidine derivs. are stated in the next chapter. Acyclovir (ACV) and ganciclovir (GCV) are pointed out in the class of acyclic nucleoside analogs as compds. which have proved to be safe and effective in therapy against herpes virus infection. In addition, emergence of resistance of herpes virus to ACV and mechanism of action of that drug on viral DNA-polymerase are described. Prodrugs of acyclic nucleosides with clin. use as valaciclovir (prodrug for acyclovir) and famciclovir (prodrug for penciclovir) are also displayed. Main goals of antiviral activity are described in the next chapter. Mol. basis of selective antiviral chemotherapy is displayed in conclusion. Use of enzyme TK HSV 1 as "suicice" **enzyme** in **combination** with fraudulent substrates in **gene therapy** of cancer and AIDS are pointed out.

L5 ANSWER 22 OF 29 MEDLINE on STN DUPLICATE 7
AB The thymidine kinase (TK) genes from herpes simplex virus (HSV) types 1 and 2 were recombined in vitro with a technique called DNA family shuffling. A high-throughput robotic screen identified chimeras with an enhanced ability to phosphorylate zidovudine (AZT). Improved clones were combined, reshuffled, and screened on increasingly lower concentrations of AZT. After four rounds of shuffling and screening, two clones were isolated that sensitize Escherichia coli to 32-fold less AZT compared with HSV-1 TK and 16,000-fold less than HSV-2 TK. Both clones are hybrids derived from several crossover events between the two parental genes and carry several additional amino acid substitutions not found in either parent, including active site mutations. Kinetic measurements show that the chimeric enzymes had acquired reduced K(M) for AZT as well as decreased specificity for thymidine. In agreement with the kinetic data, molecular modeling suggests that the active sites of both evolved enzymes better accommodate the azido group of AZT at the expense of thymidine. Despite the overall similarity of the two chimeric enzymes, each contains key contributions from different parents in positions influencing substrate affinity. Such mutants could be useful for anti-HIV **gene therapy**, and similar directed-evolution approaches could improve other **enzyme**-prodrug **combinations**.

L5 ANSWER 23 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AB Enzyme combinations useful for destroying cells, particularly proliferative cells, are disclosed. Vectors enabling the intracellular expression and transfer of said enzyme combinations, as well as the therapeutical use thereof, particularly in anti-cancer gene therapy, are also disclosed. Expression plasmids containing herpes simplex virus 1 thymidine kinase gene, Saccharomyces cerevisiae gene GUK1 guanylate kinase, and/or S. cerevisiae gene YNK nucleoside diphosphokinase were prepared Another plasmid encoding a thymidine kinase-guanylate kinase fusion protein was created. Incubation of the 3 enzymes with ganciclovir or acyclovir resulted in production of the nucleoside triphosphate analogs. Phosphorylation of ganciclovir was enhanced 1.8-fold and phosphorylation of acyclovir was enhanced 1.2-fold with the fusion protein (relative to the enzymes employed sep.).

L5 ANSWER 24 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AB A review, with 9 refs., discussing bystander effect in enzyme/prodrug gene therapy using e.g. a herpes simplex thymidine kinase/ganciclovir system. The bystander effect was so named because cells transduced with suicide gene that are dying upon treatment with the prodrug can induce the death of nontransduced neighboring cells. The combination of suicide gene therapy and immunotherapy could prevent the loss of the bystander effect via resistance or selection mechanisms. Because the elimination of a tumor is a race between tumor cell growth and cell death by treatment, any combination of approaches that enhance the killing rate should be considered.

L5 ANSWER 25 OF 29 MEDLINE on STN DUPLICATE 8
AB Expression of genes encoding prodrug-activating enzymes can increase the susceptibility of tumor cells to prodrugs, and may ultimately achieve a better therapeutic index than conventional chemotherapy. CB1954 is a weak, monofunctional alkylating agent which can be activated by Escherichia coli nitroreductase to a potent dysfunctional alkylating agent which crosslinks DNA. We have inserted the nitroreductase gene into an LNCX-based retroviral vector, to allow efficient gene transfer and expression in colorectal (LS174T) and pancreatic (SUIT2, BxPC3, and AsPC1) cancer cell lines. A clone of LS174T cells expressing nitroreductase showed > 50-fold increased sensitivity to CB1954, and nitroreductase-expressing clones of pancreatic tumor lines were up to approximately 500-fold (SUIT2) more sensitive than parental cells. Concentrations of

CB1954 minimally toxic to nontransduced cells achieved 100% cell death in a 50:50 mix of parental cells with SUIT2 cells expressing nitroreductase; and marked "bystander" cell killing was seen with just 10% of cells expressing nitroreductase. Significant bystander cell killing was dependent on a high cell density. In conjunction with regional delivery of vectors and tumor selectivity of cell entry and/or gene expression, nitroreductase and CB1954 may be an attractive **combination** for prodrug-activating **enzyme gene therapy** of colorectal and pancreatic cancer.

L5 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2005 ACS on STN
AB Chimeric genes encoding fusion proteins of enzymes that specifically activate the pyrimidine analogs 5-fluorocytosine and azidothymidine into derivs. toxic for mammalian cells are described. These genes (suicide genes) can be used singly or in combination to kill transfected tumor cells or immune cells with cell-specificity achieved by placing the genes under control of a promoter that is only active in the infected or tumor cell. Furthermore, eukaryotic vectors including two suicide gene expression units, i.e. a first unit sensitizing the tumor cells to 5-fluorocytosine or 5-fluorouracil, and a second making HIV-infected cells synergistically resistant to azidothymidine. The construction of a number of chimeric genes for fusion proteins and their use in the killing of melanoma cells in vitro is demonstrated. The cells became very sensitive to AZT and fluorocytosine.

L5 ANSWER 27 OF 29 MEDLINE on STN DUPLICATE 9
AB Derivatized bovine adenosine deaminase is used in **enzyme** replacement therapy and as an adjunct to **gene therapy** against severe **combined** immunodeficiency syndrome. Although a gene sequence is known for human adenosine deaminase, the structure of the bovine enzyme has not been characterized. Structure studies using mass spectrometry are reported here that evaluate sequence, processing, post-translational modifications and the extent of homology between the human protein and its therapeutic surrogate.

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